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FULL TEXT OF CASES (USPQ FIRST SERIES)
In re Jolles, 206 USPQ 885 (CCPA 1980)

In re Jolles

(CCPA)
206 USPQ 885

Decided July 31, 1980
No. 80-510
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Patentability -- Utility (§ 51.75)

Pleading and practice in Patent Office -- Rejections (§ 54.7)

Specification -- Sufficiency of disclosure (§ 62.7)

Absence of asserted utility may lead to rejection under either 35 U.S.C. 101 or 35 U.S.C. 112.

2. Patentability -- Evidence of -- In general (§ 51.451)

Patentability -- Utility (§ 51.75)

Proof of utility is sufficient if it is convincing to one of ordinary skill in art; amount of evidence required depends on facts of each individual case; character and amount of evidence needed may vary, depending on whether alleged utility appears to accord with or to contravene established scientific principles and beliefs.

3. Patentability -- Utility (§ 51.75)

Pleading and practice in Patent Office -- Evidence (§ 54.5)

It is proper for examiner to ask for substantiating evidence when utility as drug, medicant, or the like in human therapy is alleged, unless one with ordinary skill in art would accept allegations as obviously correct.

4. Interference -- Reduction to practice -- Tests (§ 41.758)

Patentability -- Evidence of -- In general (§ 51.451)

Patentability -- Utility (§ 51.75)

Demonstration that compound has desirable or beneficial properties in prevention, alleviation, or cure of some disease or manifestation of disease in experimental animals does not necessarily mean that compound will have same properties when used with humans, but this is by no means support for position that such evidence is not relevant to human utility; pharmacological testing in animals is relevant to utility in humans; evidence showing substantial activity against experimental tumors in mice in tests customarily used for screening of anti-cancer agents of potential

utility in treatment of humans is relevant to utility in humans and is not to be disregarded.

5. Interference -- Reduction to practice -- Tests (§ 41.758)

Operability (§ 48)

Patentability -- Utility (§ 51.75)

Board of Appeals erred by failing to give sufficient weight to similarity of remaining claimed derivatives to derivative in allowed claim when considered with animal tests.

Particular patents -- Napthacene Derivatives

Jolles, Napthacene Derivatives, rejection of claims 7-14, 16, 27-34, and 36 reversed.

Case History and Disposition:

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of George Jolles, Serial No. 652,848, filed Jan. 27, 1976. From decision rejecting claims 7-14, 16, 27-34, and 36, applicant appeals. Reversed.

Attorneys:
Ellsworth H. Mosher, Arlington, Va. (Charles A. Wendel, Arlington, Va., and Harold C. Wegner, Washington, D.C., of counsel) for appellant.

Joseph F. Nakamura (Gerald H. Bjorge, of counsel) for Commissioner of Patents and Trademarks.

Judge:
Before Markey, Chief Judge, Rich, Baldwin, and Miller, Associate Judges, and Ford, Judge. *

Opinion Text

Opinion By:
Baldwin, Judge.

This appeal is from the decision of the Patent and Trademark Office Board of Appeals (board) affirming the examiner's rejection of claims 7-14, 16, 27-34 and 36 [1] under 35 USC 101 [2] and 35 USC 112, first paragraph, [3] for lack of proof of utility. We reverse.

Background

Composition claims 7-14 and 16 encompass certain pharmaceutical compositions useful for the treatment of acute myeloblastic leukemia which comprise certain naphthacene derivatives. Method claims 27-34 and 36 encompass methods for the treatment of acute myeloblastic leukemia in a human patient by administering the subject naphthacene derivatives. Claims to the derivatives per se have been allowed in Patents No. 3,965,088 and 3,957,755. [4]

The invention is represented by generic claims 7 and 28, reproduced below. As stated explicitly in the method claims, and as recognized by appellant in his brief, the compositions are intended for use in the treatment of acute myeloblastic leukemia in human patients.

> 7. A pharmaceutical composition for parenteral administration and useful for the treatment of acute myeloblastic leukaemia which comprises, as active ingredient, a naphthacene of the formula:
> *Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
>
> wherein one of R_1 and R_2 is oxygen and the other is oxygen or = N - NHR_3, and R_3 is alkanoyl of up to 4 carbon atoms, alkanoyl of up to 4 carbon atoms substituted by a sulphonic acid group, alkanoyl of up to 4 carbon atoms sub
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>
> stituted by a quaternary ammonium group, thiocarbamoyl, methylthio-car-bamoyl, amidino, or benzoyl, or a nontoxic salt thereof, in association with a significant amount of a sterile injectable pharmaceutically-acceptable carrier.
>
> 28. Method for the treatment of acute myeloblastic leukaemia in a human patient which comprises administering parenterally to the patient a quantity of from 2 to 10 mg/kg per day of a naphthacene of the formula:
> *Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
>
> wherein one of R_1 and R_2 is oxygen and the other is oxygen or = N - NHR_3, and R_3 is alkanoyl of up to 4 carbon atoms, alkanoyl of up to 4 carbon atoms substituted by a sulphonic acid group, alkanoyl of up to 4 carbon atoms substituted by a quarternary ammonium group, thiocarbamoyl, amidino, or benzoyl, or a non-toxic salt thereof.

The derivatives bear a close structural relationship to daunorubicin [5] and doxorubicin, [6] both of which are well recognized in the art as valuable for use in cancer chemotherapy. [7]

Affidavit Evidence

Jacquillat Declarations

Two declarations by Dr. Claude Jacquillat were submitted in application Serial No. 187,559, and were before the examiner and the board in the prosecution of the subject application. Both declarations report results of clinical treatment of human patients suffering from acute myeloblastic leukemia with one of the claimed compositions. [8]The second declaration dated January 3, 1974, reports results of treatment of 100 patients under the personal supervision of Dr. Jacquillat and the method of diagnosis of acute myeloblastic leukemia, and includes the results of the treatment of 33 patients reported in the first declaration dated August 28, 1972. Dr. Jacquillat outlined the dosage rate, the length of dosage, and methods of evaluating its effect through daily blood counts and periodic bone marrow examination. Among the results reported, complete remission of the disease was achieved in 53 of the patients treated. Dr. Jacquillat concluded that the specific composition used is an active drug in the treatment of acute myeloblastic leukemia and is a valuable addition to the series of drugs available for such treatment.

Maral Declarations

Two declarations by Dr. Rene Maral were before the examiner and the board in the prosecution of the subject application. The first declaration, dated January 22, 1971, in application Serial No. 768,532, disclosed results of experimental tests with laboratory mice wherein tests for sub-acute toxicity, activity against sarcoma 180 tumors, and activity against leukemia L 1210 of seven specific compositions were

reported. The compositions tested were those described in examples 1-7 of the subject application. The seventh composition was the same composition utilized in the Jacquillat clinical tests. See n.8 supra. On the basis of reported results, Dr. Maral concluded that "the compounds of * * * Application Serial No. 768,532 have substantial activity against experimental tumours in mice in tests customarily used for the screening of anti-cancer agents of potential utility in the treatment of humans."

The second declaration, dated January 31, 1975, in application Serial No. 307,955, disclosed similar results from the same tests for sub-acute toxicity and anti-tumor activity for an additional composition corresponding to that described in example 8 of the subject application. On the basis of reported results, Dr. Maral concluded that the specific composition tested "has a substantial activity against experimental tumours in mice in tests customarily used for the screening of anti-cancer agents of potential utility in the treatment of humans."

The eight compounds tested by Dr. Maral are structurally related, the differences residing in the second C_9 substituent, being other than a hydroxy group. See claims 7 and 28 supra. Appellant provided the following tabulation of differences for the eight compounds tested.

Table set at this point is not available. See table in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

The Rejection

The examiner, relying on no prior art, rejected claims 7-16 and 27-36 under 35 USC 101 and 35 USC 112, first paragraph, "for lack of proof of utility." The examiner, in her answer, found there was "insufficient evidence of operativeness in the record that the various compositions are safe and effective to treat acute myeloblastic leukaemia in human patients," citing In re Citron, 51 CCPA 852, 325 F.2d 248, 139 USPQ 516 (1963), for support. The examiner further asserted:

> The instant claims are directed to an incredible utility. The method of treating a human leukaemia and a pharmaceutical composition for this use employing appellant's naphthacene compounds have not been set forth in the specification as required by the statute. There are no specific examples or test data showing the effectiveness of the claimed pharmaceutical compositions for the alleged use which would include a specific dosage for a specific patient and duration of treatment. The dosage range given for the active ingredient, i.e. the naphthacene compound in the composition is 2-10 mg./kg. per day. It is not stated in the specification, however, whether the dosage should be given periodically or in a single dose, nor what a total dosage should be. Accordingly, appellant has not made known exactly how his invention is to be used, but rather, has left the matter of how to use to speculation. * * *
>
> The Declaration of Dr. Jacquillat * * * has again been carefully considered, but is not convincing. The Declaration shows the use of only one of the compounds used in appellant's invention, which is the pharmaceutical composition of claim 15 and the method of claim 35. This compound is referred to as product "g" in the Declaration which shows that out of 100 patients treated with product "g", only 53 (53%) had complete remission after 30 to 40 days of treatment * * *. The remission was not of long duration as shown in Table II of the Declaration. Table I of the Declaration shows that death occurred in thirteen adults during induction of the treatment. Therefore, this data is not deemed persuasive that product "g", the compound used in claims 15 and 35, is safe and effective for treating acute myeloblastic leukaemia in humans.
>
> With regard to the various other naphthacene compounds employed in appellant's methods and compositions of claims 7-14, 16-34 and 36, due to the unpredictability of chemical compounds and side reactions, and therapeutic conditions such as leukaemia, it would not be reasonable for a person of ordinary skill in the art to presume that these novel compounds would be safe and effective for the

> incredible utility alleged in the absence of verified data substantiating the said allegations of use.

The Board

The board sustained the rejection of claims 7-14, 16, 27-34 and 36 but not the rejection of claims 15 and 35. The board reasoned as follows:

> We have carefully considered all of the arguments and evidence and conclude that the results set forth in the Maral declaration exhibit effectiveness for each of the claimed compositions with respect to the treatment of experimental tumors, i.e., sarcoma 180 and leukemia L1210 in mice and hence establish the utility of the compositions in mice. * * * We think it is clear from appellant's remarks that the present claims on appeal contemplate only human utility. In that regard, the Maral evidence is not relevant.

With respect to the additional evidence set forth in the declarations of Professor Jacquillat regarding the treatment of humans afflicted with acute myeloblastic leukemia, we find that only one compound was tested relating to the operativeness of the claimed subject matter. In carefully evaluating the Jacquillat evidence, we observe that the active ingredient of claims 15 and 35 administered in the manner taught in the specification is useful to some degree inasmuch as remissions in 53% of the patients were achieved and we therefore conclude that the operativeness of said compound is sufficiently established to satisfy the requirements of 35 USC 101 and the first paragraph of 35 USC 112. With respect to the Examiner's contention that it has not been demonstrated that the claimed invention is safe, we refer to In re Anthony, 56 CCPA 1443, 414 F.2d 1383, 162 USPQ 594 (1969) and In re Watson, 517 F.2d 465, 186 USPQ 11 (CCPA 1975) which hold that claims may satisfy the requirements of 35 USC 101 for utility despite the lack of safety. * * *

The Jacquillat evidence, however, which is limited to one compound is insufficient to satisfy the requirements of 35 USC 101 with respect to the remaining claims in view of the nature of the utility and the scope of the claims. There is no indication that the compounds of claims 7 to 14, 16, 27 to 34 and 36 which differ in structure from the benzoyl-hydrazono compound of claims 15 and 35 are effective in the treatment of acute myeloblastic leukemia. Appellant appears to rely upon the analogy with the known compounds "daunorubicin and doxorubicin" to provide the utility requirements for all the compositions. The claimed products differ from the aforesaid prior art compounds in the replacement of keto groups at C-9 and/or at one of C-5 and C-12 positions with an = N-NH-R_3 grouping, wherein R_3 is set forth as a variety of substituents. We note that the Examiner has reviewed the prior art as represented by the Arcamone et al. patents [9] and determined that the claimed compositions were not prima facie obvious therefrom. We cannot conclude that the claimed compositions are so similar to those of the prior art as to expectedly have the same specific utility of treating acute myeloblastic leukemia in humans. On the record before us, considering the nature of the stated utility, we cannot conclude that appellant has submitted sufficient evidence of demonstrated utility commensurate with the scope of the claims. We find the quantum of evidence represented by a single compound falls far short in proving the asserted utility.

Opinion

[1] While the rejection below was under both 35 USC 101 and 35 USC 112, first paragraph, the dispositive issue is whether appellant has submitted sufficient evidence to establish his asserted utility of the compositions and methods of the rejected claims for the treatment of acute myeloblastic leukemia in human patients. [10] The examiner in her rejection raised questions on the legal adequacy of appellant's disclosure of how to use the claimed compounds under 35 USC 112, first paragraph, viz., the specific dosage and duration of treatment, but the board has specifically rejected this argument with regard to claims 15 and 35, and the solicitor does not argue this further in his brief. Accordingly, we consider the rejection under both provisions to turn on the proof of utility issue.

The contents of the declarations in the record and the qualifications of the declarants have not been challenged, so we accept their contents and conclusions at face value.

[2] Proof of utility is sufficient if it is convincing to one of ordinary skill in the art. In re Irons, 52 CCPA 938, 340 F.2d 974, 144 USPQ 351 (1965). The amount of evidence required depends on the facts of each individual case. In re Gazave, 54 CCPA 1524, 379 F.2d 973, 154 USPQ 92 (1967). The character and amount of evidence needed may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs.

In re Chilowsky, 43 CCPA 775, 229 F.2d 457, 108 USPQ 321 (1956).

The examiner in her rejection referred to the "incredible utility" of the subject claims. The solicitor in his brief further argues that "[a]t best the asserted usefulness here is highly speculative and against the grain of human experience. At worst it is incredible." Neither the solicitor nor the examiner provides support for the assertion regarding "incredible utility." Such assertions have been readily rebutted by the Jacquillat evidence together with the known utility of daunorubicin and doxorubicin, which clearly establish that the medical treatment of a specific cancer is not such an inherently unbelievable undertaking or involves such implausible scientific principles as to be considered incredible.

[3] The board avoided the examiner's assertion of incredible utility, but did question the operativeness of the claimed subject matter. When utility as a drug, medicant, and the like in human therapy is alleged, it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct. In re Novak, 49 CCPA 1283, 306 F.2d 924, 134 USPQ 335 (1962).

However, in considering the evidence proferred by appellant, the board dismissed the Maral declarations as not relevant to establish the claimed human utility. The Jacquillat clinical tests were accepted by the board solely for the establishment of utility for the specific composition tested.

[4] We believe the board erred in dismissing the Maral evidence as not relevant to human utility. This court recognizes "that a demonstration that a compound has desirable or beneficial properties in the prevention, alleviation, or cure of some disease or manifestation of a disease in experimental animals does not necessarily mean that the compound will have the same properties when used with humans." In re Krimmel, 48 CCPA 1116, 1123, 292 F.2d 948, 953, 130 USPQ 215, 219 (1961). However, this is by no means support for the board's position that such evidence is not relevant to human utility.

To the contrary, this court has accepted tests on experimental animals as sufficient to establish utility in In re Bergel, 48 CCPA 1102, 292 F.2d 955, 130 USPQ 206 (1961). Utility was recognized by this court in Bergel not because of any concern with the health or existence of the experimental animals, but rather because of the widespread pharmacological work in animals recognized as a screening procedure for testing new drugs. It is clear that such testing is relevant to utility in humans. Evidence showing substantial activity against experimental tumors in mice in tests customarily used for the screening of anticancer agents of potential utility in the treatment of humans is relevant to utility in humans and is not to be disregarded. In re Buting, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689 (1969).

[5] The board, after evaluating the Jacquillat evidence, concluded that the operativeness of the specific derivative utilized in the Jacquillat clinical tests was sufficiently established to satisfy the utility requirements of sections 101 and 112, first paragraph, and accordingly did not sustain the examiner's rejection of claims 15 and 35. However, the board found the quantum of evidence represented by the single derivative to fall far short in proving the asserted utility for the remaining claimed derivatives. The board erred in this finding by failing to give sufficient weight to the similarity of the remaining claimed derivatives to the derivative in allowed claims 15 and 35 when considered with the Maral animal tests.

The similarities of the claimed derivatives to each other are represented in the tabulation of differences provided supra for the eight compounds tested by Dr. Maral. The Maral declarations establish that the eight compounds have substantial activity against experimental tumors in mice. The board found that the successful clinical tests in humans of the one derivative shown in the Jacquillat declarations sufficiently established utility for claims 15 and 35. The claimed compounds have a close structural relationship to daunorubicin and doxorubicin, both known to be useful in cancer

chemotherapy. Considering these facts in the record before us, we conclude that one of ordinary skill in the art would accept appellant's claimed utility in humans as valid and correct.

The decision of the board is *reversed.*

Reversed

Footnotes

Footnote 1. The claims appear in application Serial No. 652,848 (subject application), filed January 27, 1976, and entitled "Naphthacene Derivatives." The application is a division of Serial No. 307,955, filed November 20, 1972, now Patent No. 3,965,088, which in turn is a continuation-in-part of Serial No. 187,559, filed October 7, 1971, now Patent No. 3,957,755, which in turn is a continuation-in-part of Serial No. 768,532, filed October 17, 1968, now abandoned.

Footnote 2.

35 USC 101 provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Footnote 3.

35 USC 112, first paragraph, provides:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Footnote 4.

See n.1 supra.

Footnote 5.

Daunorubicin:
Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

Footnote 6. Doxorubicin, also referred to as adriamycin, U.S. Patent
Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

Footnote 7.

The Merck index refers to each of these as "antineoplastic," i.e., antagonistic with respect to the formation of new growths.

Footnote 8.

Claims 15 and 35, which stand allowed, are directed to the specific pharmaceutical composition and corresponding method for treatment reported by Dr. Jacquillat in his declarations. Claim 15 reads:

15. A composition according to Claim 7 in which active ingredient is 4-methoxy-5, 12-dioxo-6,9,11-trihydroxy-7- (2,3,3-0-tridesoxy-3-amino-l-L-lyxohexosyl)-9-[l-(benzoylhydrazono)ethyl]-5,7,8, 9,10,12-hexahydronaphthacene, or a non-toxic acid addition salt thereof.

Footnote 9. The Arcamone et al. patents, U.S. Patents No. 3,590,028 and 3,686,163, were cited as prior art references in the prosecution of U.S. Patents No. 3,957,755 and 3,965,088, wherein claims for the naphthacene derivative compositions per se were allowed. See n.1 supra.

Footnote 10. Absence of asserted utility may lead to a rejection under either 35 USC 101 or 35 USC 112. In re Gardner, 475 F.2d 1389, 1392, 177 USPQ 396, 398 (CCPA 1973).

Footnote * The Honorable Morgan Ford, United States Customs Court, sitting by designation.

- End of Case -

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